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Gene-Environment Interaction in the Onset of Eczema in Infancy: Filaggrin Loss-of-Function Mutations Enhanced by Neonatal Cat Exposure

Hans Bisgaard1*, Angela Simpson2, Colin N.A. Palmer3, Klaus Bønnelykke1, Irwin Mclean3, Somnath Mukhopadhyay4, Christian B. Pipper1, Liselotte B. Halkjaer1, Brian Lipworth5, Jenny Hankinson2, Ashley Woodcock2, Adnan Custovic2

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ABSTRACT

Background

Loss-of-function variants in the gene encoding filaggrin (FLG) are major determinants of eczema. We hypothesized that weakening of the physical barrier in FLG-deficient individuals may potentiate the effect of environmental exposures. Therefore, we investigated whether there is an interaction between FLG loss-of-function mutations with environmental exposures (pets and dust mites) in relation to the development of eczema.

Methods and Findings

We used data obtained in early life in a high-risk birth cohort in Denmark and replicated the findings in an unselected birth cohort in the United Kingdom. Primary outcome was age of onset of eczema; environmental exposures included pet ownership and mite and pet allergen levels. In Copenhagen (n = 379), FLG mutation increased the risk of eczema during the first year of life (hazard ratio [HR] 2.26, 95% confidence interval [CI] 1.27–4.00, p = 0.005), with a further increase in risk related to cat exposure at birth amongst children with FLG mutation (HR 11.11, 95% CI 3.79–32.60, p < 0.0001); dog exposure was moderately protective (HR 0.49, 95% CI 0.24–1.01, p = 0.05), but not related to FLG genotype. In Manchester (n = 503) an independent and significant association of the development of eczema by age 12 mo with FLG genotype was confirmed (HR 1.95, 95% CI 1.13–3.36, p = 0.02). In addition, the risk increased because of the interaction of cat ownership at birth and FLG genotype (HR 3.82, 95% CI 1.35–10.81, p = 0.01), with no significant effect of the interaction with dog ownership (HR 0.59, 95% CI 0.16–2.20, p = 0.43). Mite-allergen had no effects in either cohort. The observed effects were independent of sensitisation.

Conclusions

We have demonstrated a significant interaction between FLG loss-of-function main mutations (501x and 2282del4) and cat ownership at birth on the development of early-life eczema in two independent birth cohorts. Our data suggest that cat but not dog ownership substantially increases the risk of eczema within the first year of life in children with FLG loss-of-function variants, but not amongst those without. FLG-deficient individuals may need to avoid cats but not dogs in early life.

The Editors' Summary of this article follows the references.
Introduction

We recently discovered in the Copenhagen Prospective Study on Asthma in Childhood (COPSAC) that loss-of-function variants in the gene encoding filaggrin (FLG) are major determinants of eczema [1]. This finding has since been replicated in other populations [2–4], and the population attributable risk for eczema estimated at 11% [2].

FLG is situated in the Epidermal Differentiation Complex, a dense cluster of genes on Chromosome 1q21. It codes for the 500-kDa protein profilaggrin, which is the main protein component of the keratohyalin granules within the outermost living cell layers of the epidermis. During terminal differentiation of keratinocytes, profilaggrin is dephosphorylated into filaggrin peptides (37-kDa proteins), which form highly compacted, chemically cross-linked layers that provide a physical barrier that reduces water loss and protects the body from potentially harmful environmental exposures. Nonsense mutation R501X and frame-shift mutation 2282del4 lead to complete loss of filaggrin expression [5], which causes excessively dry skin and impaired skin barrier function. We hypothesized that weakening of skin barrier function in filaggrin-deficient individuals may modulate the effect of environmental exposures, thus modifying the expression of eczema. Since most eczema in individuals with FLG mutations occurs within the first year of life, the important environment exposures that may affect the penetrance of FLG mutations are likely to occur in the first months of life. We therefore investigated whether there is an interaction between FLG loss-of-function mutations with early-life environmental exposures (pets and dust mites) in relation to the development of eczema. We used data obtained in a high-risk birth cohort in Denmark, and in an unselected birth cohort in the UK.

Methods

COPSAC

COPSAC enrolled 411 high-risk neonates (mother with verified asthma) at age 1 mo; the recruitment was previously described in detail [6–8]. The study was approved by the Ethics Committee for Copenhagen (KF 01–289/96) and The Danish Data Protection Agency (2008-41-1754). Before enrolment, informed consent was obtained from parents. Data were collected on-line and locked after external monitoring. An audit trail was run routinely.

Primary outcome. Eczema was diagnosed on clinical examination in participants who were assessed at the COPSAC Clinical Research Unit at age 1 mo, and at 6-mo intervals thereafter; additional visits were arranged immediately upon the onset of any skin or respiratory symptoms. Skin examinations, diagnoses, and treatment of eczema were carried out by trained study physicians. Skin lesions were described on-line according to predefined morphology and localization; eczema was defined based on the Hanifin-Rajka criteria as previously detailed [9,10].

Secondary outcome. Allergic sensitisation was defined as specific IgE > 0.35 kU/l to a range of common inhalant and food allergens at age 6 and 18 mo (ImmunoCAP, Phadia) [11].

Environmental exposures. Pet exposure in early life was assessed by questionnaires administered during the home visit carried out within 4 wk after birth and defined as the presence of a cat or a dog in the house at birth. Allergen exposure was measured in dust samples collected at age 1 y by vacuuming 1 m² of living-room floor for 2 min. Mite, cat, and dog allergen was quantitated using enzyme-linked immunoassays; results were expressed as allergen concentration (µg/g).

FLG Genotyping

Genotyping for R501X was performed using a TaqMan®-based allelic discrimination assay (Applied Biosystems). Allelic discrimination was assessed using Applied Biosystems 7700 sequence detection system. Probes and primers were as described [1]. Mutation 2282del4 was genotyped by sizing of a fluorescent-labeled PCR fragment on an Applied Biosystems 3100 or 3730 DNA sequencer [1].

Statistical Analysis

Children were classified according to a two level dominant genetic model (i.e., children were assigned as having a FLG mutation if they were heterozygous or homozygous for the null allele in at least one of the two SNPs).

Effects of environmental factors and their possible modification by genetic mutation were assessed by Kaplan-Meier curves and Cox regression. The children were retained in the analysis from birth until age at diagnosis of eczema, drop-out, or age 1 y, whichever came first. Simultaneous quantification of geneenvironment effects was done by multiple Cox regression. Pet exposure at birth and pet allergen exposure were analysed separately. All analyses were carried out using SAS 9.1.3, SPSS 13.0, and the free-ware statistical package R (R Development Core Team, 2006). All estimates are reported with 95% confidence intervals [CI] in brackets.
Results

The effects from FLG mutations in both cohorts occurred early in life as demonstrated by the Kaplan Meier curves (Figures 1 and 2), with hazard ratios (HR) of 2.90 (1.80–4.68) and 2.06 (1.40–3.05) in the first year and 0.71 (0.22–2.27) and 1.01 (0.48–2.51) after age 1 y (COPSAC and MAAS, respectively). We therefore focused the analysis on the interaction between FLG status and environmental exposures during the first year of life. Exposure variables in both cohorts were independent of FLG mutations.

COPSAC

Of 411 infants, 379 of mixed European ancestry were genotyped for 501x and 2282del4 [1] as well as R2448X and S3247X [15]. The main mutated alleles 501x and 2282del4 were present in 40 children and exhibited a very strong association to the development of eczema as previously reported [1].

Eczema was diagnosed in 28% (105 children) before age 1 y; 265 (75%) did not have pets in their home at birth, 38 (11%) had a cat, 37 (11%) had a dog, and 11 (3%) had both; information on pet ownership was not available in 28 children. Among the 38 children with main mutations and information on pet ownership, 26 (68%) did not have pets, seven (18%) had a dog only, four (11%) had a cat only, and one (3%) had both. Objective measure of allergen exposure was available in 339 children; 205 (60%) had low cat and dog allergen levels, 54 (16%) high cat allergen level, 54 (16%) high dog allergen level, 26 (8%) high cat and dog allergen levels, and 78 (23%) high mite allergen level. Among the 38 children with mutation, 22 (58%) had low cat and dog allergen levels, five (13%) high cat allergen level, nine (24%) high dog allergen level, two (5%) had high cat and dog allergen levels, and ten (26%) high mite allergen level. Six children were lost to follow-up during the first year but were included in the analyses for the available follow-up period.

Kaplan-Meier plots suggested an increased risk of eczema due to FLG mutation, and a further increased risk of eczema due to cat exposure but only in the presence of FLG mutation (Figure 3). Backwards elimination in a multiple Cox regression including FLG status, cat exposure, dog exposure, mite allergen exposure, and interactions between FLG status and cat exposure, dog exposure, and mite allergen exposure showed a significant interaction between cat exposure and FLG status (p = 0.0008) and a significant effect of dog exposure (p = 0.05). An additional exploration of the cat exposure-FLG status interaction demonstrated an increased risk of developing eczema due to mutation (HR 2.26 [95% CI 1.27–4.00], p = 0.005), with an additional increased risk if also exposed to cat (HR 11.11 [3.79–32.60], p < 0.0001). The overall decrease in risk due to exposure to dog was quantified in an HR of 0.49 [0.24–1.01]. Analysis including only children carrying mutant alleles demonstrated a significant effect of cat ownership on development of eczema (HR 7.49 [2.37–23.67], p = 0.0006).

For allergen exposure a similar analysis was made with cat, dog, and mite allergen levels. The model confirmed an increased risk of developing eczema due to mutation (HR 2.53 [1.45–4.41], p = 0.001) with an additional increase in risk if exposed to high cat allergen level (HR 3.77 [1.45–9.81], p = 0.006). In this analysis there was no significant effect of dog or mite allergens. Analysis including only children carrying mutant alleles demonstrated a significant effect of cat allergen exposure on development of eczema (HR 3.09 [1.17–8.19], p = 0.029).

Cat allergen exposure shows high agreement with reported cat exposure at 4 wk (simple Kappa coefficient 0.62 [0.51–0.73]). Similarly dog allergen exposure shows high agreement...
with reported dog exposure at 4 wk (simple Kappa coefficient 0.59 [0.48–0.70]).

*S. aureus* was identified from the perineum in one newborn before the age of 3 mo.

MAAS

Of 940 children with questionnaire data on the age of onset of eczema, 513 provided a blood sample for DNA extraction. Children who provided DNA did not differ from those who did not in terms of family history, maternal age, socio-economic status, history of eczema, allergic sensitisation, and pet ownership (data available on request).

A total of 503 children of mixed European ancestry had information on *FLG* main mutations (501x and 2282del4), pet ownership at birth, and the age of onset of eczema. By age 1 y, eczema was reported by 187/503 parents (37%). Mutated alleles were present in 50 children (10%); 324 (64%) did not own any pets at birth, 88 (18%) had a cat at home, 66 (13%) had a dog, and 25 (5%) had both. The frequency of pet ownership did not differ between children with or without *FLG* mutation (no pets 293/453 [64.7%] and 31/50 [62%], cat 77/453 [17%] and 11/50 [22%], dog 60/453 [13.2%] and 6/50 [12%], and both cat and dog 23/453 [5.1%] and 2/50 [4%], no *FLG* mutation versus *FLG* mutation, respectively, *p* = 0.84). Cat allergen exposure was available in 461 children, mite allergen in 458, and dog allergen in 460.

Kaplan-Meier plots demonstrating the age of onset of eczema in the first year of life related to cat and dog ownership amongst children with and without *FLG* mutation are presented in Figure 4. The results of a multiple Cox regression that included *FLG* genotype, cat and dog ownership at birth, the interaction between *FLG* genotype with cat and dog ownership, and mite exposure and its interaction with *FLG* genotype indicated an increased risk of developing eczema in the first 12 mo due to *FLG* mutation (HR 1.95 [95% CI 1.13–3.26], *p* = 0.017). Furthermore, in the presence of *FLG* mutation, the risk increased further because of cat ownership at birth, with no significant effect of cat ownership being observed amongst children without *FLG* mutation (interaction of cat ownership at birth and *FLG* mutation, HR 3.82 [1.35–10.81], *p* = 0.011). There was a trend for dog ownership to increase the risk (HR 1.51 [0.96–2.37], *p* = 0.075), with no significant interaction of *FLG* genotype with dog ownership (HR 0.59 [0.16–2.20], *p* = 0.43) or mite allergen exposure (HR 1.15 [0.93–1.43], *p* = 0.21). There was no significant effect of having both cats and dogs (HR 1.57 [0.82–3.03]), or their interaction with *FLG* genotype (*p* = 0.96). Analysis including only children carrying mutant alleles demonstrated a significant effect of cat ownership on development of eczema (HR 2.47 [1.09–5.62], *p* = 0.03).

In terms of allergen exposure there was no significant correlation between mite, cat, and dog allergen levels. Multiple Cox regression that included *FLG* genotype, cat, dog, and mite allergen levels, and the interaction between genotype and allergen levels confirmed an increased risk of developing eczema due to mutation (HR 2.22 [1.27–3.89], *p* = 0.005) and the interaction between cat allergen and *FLG* genotype (with risk increasing risk with increasing allergen level among children with *FLG* mutation; HR for interaction 1.31 [1.03–1.67], *p* = 0.026). Nonsignificant trends were observed for dog allergen exposure (HR 1.07 [1.00–1.15], *p* = 0.06), the direction of which appeared to inverse in the interaction with *FLG* mutation (0.84 [0.68–1.05, *p* = 0.1]).

Secondary outcomes. Allergic sensitisation was uncommon in early life in both cohorts (in COPSAC, cat sensitisation was detected in one infant with *FLG* mutation at 6 mo but none at 18 mo; in MAAS, two children were skin test positive to mite, four to cat, and three to dog at age 1 y). We therefore did not analyse sensitisation further.

**Discussion**

**Principal Findings**

We have demonstrated a significant interaction between *FLG* loss-of-function main mutations (501x and 2282del4) and cat ownership at birth on the development of early-life...
eczema in two independent birth cohorts. Our data suggest that cat but not dog ownership substantially increases the risk of eczema within the first year of life in children with FLG loss-of-function variants, but not amongst those without. The observed effects were independent of allergic sensitisation.

For the primary outcome we selected age of onset of early eczema. The rationale for this is that in both cohorts the increased risk of eczema amongst FLG mutation carriers occurred only in the first year of life and not thereafter (Figures 1 and 2). Therefore development of eczema during the first year of life is the relevant outcome when studying this gene-environment interaction. This also means that the important environmental exposures that may interact with FLG in the development of eczema must occur in the first months of life. This limits the number of relevant exposures, as neonates typically live in a very sheltered environment.

Limitations and Strengths

This was a hypothesis-driven analysis. We hypothesized that weakening of physical barrier of skin in FLG deficient individuals may potentiate the effect of relevant environmental exposures. Therefore we investigated whether there is an interaction between FLG loss-of-function mutations with a range of environmental exposures for which the skin could be the relevant route of exposure. Since FLG is not expressed in either lungs or GI tract, we did not test exposures through such routes. We focused on the exposure that was associated with eczema in previous epidemiological studies and that was common for the two populations tested (domestic pets and indoor allergens). In addition, in COPSAC we explored the possibility of testing the effect of skin colonization with S. aureus, but only one child in the mutated group was colonized on the skin.

The different designs of the two cohorts prevented data pooling in favour of replication, and necessitated some differences in data analysis. Clinical outcomes were not identical, resulting in a higher prevalence of infant eczema in MAAS (parentally reported, 37%) compared to COPSAC (investigator-diagnosed, 28%). This suggests that MAAS was capturing milder cases and overreporting of eczema by parents. COPSAC provided closely monitored prospective data on eczema progression. The specificity of diagnosis was high, since the detailed phenotyping and management was carried out solely by the investigators, reducing the risk of misclassification [9], which is of particular importance in the clinical evaluation of eczema where interobserver variation is a problem [16]. Despite the differences in definition of primary outcome, we achieved replication.

We acknowledge the fact that the initial finding is based on only five children with eczema with a cat at home and carrying FLG mutation in COPSAC, but the power of the statistics ($p < 0.0001$) derives from the longitudinal dataset with the time of onset clearly distinguishing these populations. Cross-sectional analyses would not have such statistical power. Furthermore, it is worth noting that the findings were confirmed in the analysis of allergen levels, that pet ownership did not differ between those with and without the variant, and that the interaction between FLG variants and cat ownership was replicated in an independent cohort that included a larger number of cat exposed FLG mutation carriers.

Allergens levels were measured at age 1 y representing allergen exposure during the first year of life. Dust samples were taken from the child’s mattress in COPSAC and from the lounge floor in MAAS, which resulted in different distribution of results (10-fold increase from third to fourth quartile in COPSAC with only 3-fold difference in MAAS, indicating that quartile analysis would not be appropriate in MAAS). Although we used different indices of allergen exposure, we obtained similar results.

In the original discovery in COPSAC of the loss-of-function variants 501x and 2282del4 in the gene encoding filaggrin, we demonstrated a strong association to the development of eczema in the first years of life. Two new SNPs within the filaggrin gene (R2447X and S3247X) have since been reported [15] and were found in eight children in COPSAC. However, these new SNPs are qualitatively different from the old mutations with some residual function as demonstrated by a significantly lower penetrance of eczema. Inclusion of the

Figure 4. MAAS: Kaplan-Meier Estimates of Cumulative Risk of Eczema during the First Year of Life Stratified on Mutation and Cat at Birth Status

Numbers at risk at birth, 6, and 12 mo are given below the graph.

(A) No FLG mutation.

(B) FLG mutation.

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novel SNPs would therefore weaken our analyses by mixing a well-known strong risk factor with a weak risk factor, which furthermore is qualitatively different and therefore may have a different effect on the gene–environmental interactions studied. As a consequence we did not find it reasonable to formulate a dominant genetic model based on all four SNPs.

Meaning of the Study

Several studies have suggested an effect of early-life pet exposure on the development of atopic disease. However, the data are inconsistent, with some studies showing increased risk [17], and others decreased risk [18], or no effect [19]. These inconsistencies may be due in part to epidemiological artifacts. Recall bias is an obvious risk when exposure assessments are retrospective. Selection for keeping pets is another potential bias. The time from exposure to assessment of the health outcome has been long in some studies, which may lead to confounding by early modification of the exposure and therefore affect the long-term outcome. The causal-effect direction may be uncertain in retrospective assessments, as the pets may have been acquired after the disease onset. Furthermore, cross-sectional studies may report protective effects from pet exposure, when in fact individuals have removed the pet from the household because of the disease or the factors associated with a predisposition to disease. Importantly, in both our studies we documented pet exposure at birth (i.e., before eczema occurrence), thus eliminating uncertainty of the direction of association between exposure and disease. The findings were further supported by objective measures of allergen exposure.

We only assessed animals living in the household, though other exposures outside the home may be relevant, but this would only have biased the risk estimates toward the null, potentially underestimating the true risk. Having pets has been reported to be biased from socioeconomic status, smoking habits, and parental allergic rhinitis [20], but it is unlikely to affect the genetic distribution in the study population and could therefore not act as confounder.

The mechanism by which cat exposure drives the development of eczema is unknown. Our data suggest that it does not act through cat-specific immunoglobulin E (IgE). This is in keeping with previous studies showing that the effect of FLG loss-of-function mutations was equally strong on allergic and nonallergic eczema, demonstrating that the development of eczema is not dependent on allergic sensitisation [2]. Cat exposure may act through other nonallergic mechanisms such as endotoxins. COPSAC recently reported that bacterial colonization of the airways in neonates was associated with later development of recurrent wheeze, asthma, and increased total immunoglobulin E (IgE) [8]. It may be possible that cat exposure mediates its effect in the FLG mutated genotypes via altered bacterial exposure, or that cat exposure may be a surrogate marker for other unknown environmental influences penetrating the imperfect skin barrier because of defective profilaggrin synthesis.

Conclusions

Although there are many new susceptibility genes for complex disorders following genome-wide association studies, there are very few gene-environment studies. Our findings of a consistent effect from early-life cat ownership on the phenotypic expression of eczema in infants with FLG loss-of-function mutations in two independent birth cohorts is an example of gene–environment interaction in a common complex disease, demonstrating that such gene–environment interactions exist and are detectable given appropriately detailed studies of environmental exposures.

Editors’ Summary

Background. Eczema is a skin condition characterized by dry, red, and itchy patches on the skin. Eczema is associated with asthma and allergy, though allergy rarely plays a role in development or severity of eczema. Eczema usually begins during infancy, typically on the face, scalp, neck, extensor sides of the forearms, and legs. Up to one in five infants develops eczema, but in more than half of them, the condition improves or disappears completely before they are 15 years old. If eczema persists into adulthood, it usually affects the face and the skin inside the knees and elbows. There is no cure for eczema but it can be controlled by avoiding anything that makes its symptoms worse. These triggers include irritants such as wool, strong soaps, perfumes, and dry environments. A good skin-care routine and frequent moisturizing can also help to keep eczema under control, but in many cases, corticosteroid creams and ointments may be necessary to reduce inflammation.

Why Was This Study Done? Eczema tends to run in families. This suggests that eczema is caused by genetic factors as well as by environmental factors. Recently, researchers discovered that two common “loss-of-function” variants in the gene encoding filaggrin (FLG) predispose people to eczema. People who inherit one or two defective genes make no filaggrin, a protein that normally forms a physical barrier in the skin that protects the body from potentially harmful substances in the environment. Might the weakening of this barrier in filaggrin-deficient individuals affect their responses to environmental substances to which the skin is exposed? In this study, the authors test this potential explanation for how genetic and environmental factors (in particular, exposure to pets) might interact to determine an individual’s chances of developing eczema.

What Did the Researchers Do and Find? To test their hypothesis, the researchers studied two independent groups of infants during their first year of life—a high-risk group consisting of infants born in Copenhagen, Denmark to mothers with asthma and a group of infants born to women from the general population in Manchester, United Kingdom. The researchers determined which FLG variants each child had inherited and classified those with either one or two defective copies of FLG as having an FLG mutation. They determined pet exposure in early life by asking whether a dog or a cat was living in the parental home when the child was born (“pet ownership”) and then analyzed how these genetic and environmental factors affected the age of onset of eczema. In both groups, children with FLG mutations were twice as likely to develop eczema during the first year of life as children without FLG mutations. For children without FLG mutations, cat ownership at birth had no effect on eczema risk but for children with FLG mutations, cat ownership at birth (but not dog ownership) further increased the risk of developing eczema.

What Do These Findings Mean? These findings show that FLG mutations and cat ownership at birth interact to determine the chances of a child developing eczema during the first year of life. They provide support, therefore, for the researchers’ suggestion that the weakening of the skin’s protective barrier that is caused by filaggrin deficiency increases the child’s susceptibility to factors associated with cat exposure. Only a small number of children in this study carried FLG mutations and were exposed to cats from birth, so these findings need confirming in independent studies. In addition, it is still not clear how exposure to cats drives the development of eczema. Allergy was not the mechanism as the FLG-deficient children exposed to cat and who developed eczema did not develop cat-specific immunoglobulin E antibodies. Nevertheless, these findings suggest that, to reduce their risk of developing eczema, filaggrin-deficient individuals should avoid cats (but not dogs) during the first few months of life.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.0050131.

- The MedlinePlus Encyclopedia has a page on eczema (in English and Spanish); links to further information are provided by MedlinePlus.
- EczemaNet is a comprehensive online information resource about eczema provided by the American Academy of Dermatologists.
- The US National Institute of Arthritis and Musculoskeletal and Skin Diseases provides information on eczema.
- The UK National Health Service Direct health encyclopedia provides information for patients on eczema (in several languages).
- The Copenhagen Studies on Asthma in Childhood (COPSAC) and Manchester Asthma and Allergy Study (MAAS) Web sites provide more information about the children involved in this research.